2 micrograms/mL 10 hours after injection. A plasma concentration of 38 micrograms/mL has been reported after the intravenous infusion of 500 mg over 30 minutes, reducing to 18 micrograms/mL 1 hour later. Amikacin has been detected in body tissues and fluids after injection; it crosses the placenta but does not readily penetrate into the CSF, although substantial penetration of the blood-brain barrier has been reported in children with meningitis.

A plasma half-life of about 2 to 3 hours has been reported in patients with normal renal function. Most of a dose is excreted by glomerular filtration in the urine within 24 hours.

◊ References.

1. Vanhaeverbeek M, *et al*. Pharmacokinetics of once-daily amikacin in elderly patients. *J Antimicrob Chemother* 1993; **31:** 185–7.
2. Gaillard J-L, *et al*. Cerebrospinal fluid penetration of amikacin in children with community-acquired bacterial meningitis. *Antimicrob Agents Chemother* 1995; **39:** 253–5.
3. Bressolle F, *et al*. Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother* 1996; **40:** 1682–9.
4. Canis F, *et al*. Pharmacokinetics and bronchial diffusion of single daily dose amikacin in cystic fibrosis patients. *J Antimicrob Chemother* 1997; **39:** 431–3.
5. Tod M, *et al*. Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. *Antimicrob Agents Chemother* 1998; **42:** 849–56.
6. Tréluyer JM, *et al*. Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants, and children. *Antimicrob Agents Chemother* 2002; **46:** 1381–7.

Uses and Administration

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin and is used similarly to gentamicin (p.284) in the treatment of severe Gram-negative and other infections. It is given as the sulfate, and is generally reserved for the treatment of severe infections caused by susceptible bacteria that are resistant to gentamicin and tobramycin. Amikacin has also been given with antimycobacterials in the treatment of nontuberculous mycobacterial infections (p.181). As with gentamicin, amikacin may be used with penicillins and with cephalosporins; the injections should be given at separate sites.

Doses of amikacin sulfate are expressed in terms of amikacin base; 1.3 g of amikacin sulfate is equivalent to about 1 g of amikacin. Adults and children may be given 15 mg/kg daily in equally divided doses every 8 or 12 hours by intramuscular injection. In life-threatening infections, the dose may be increased in adults up to a maximum of 500 mg every 8 hours. A dose of 7.5 mg/kg daily in two divided doses (equivalent to 250 mg twice daily in adults) may be given for the treatment of uncomplicated urinary-tract infections. The same doses may be given by slow intravenous injection over 2 to 3 minutes, or by intravenous infusion. In adults, 500 mg in 100 to 200 mL of diluent has been infused over 30 to 60 minutes; proportionately less fluid should be given to children.

Neonates may be given 10 mg/kg as a loading dose, followed by 15 mg/kg daily in two divided doses. If given by intravenous infusion, an infusion period of 1 to 2 hours is recommended. It has been suggested that doses may need to be adjusted in preterm neonates.

Treatment should preferably not continue for longer than 7 to 10 days, and the total dose given to adults should not exceed 15 g. Peak plasma concentrations greater than 30 to 35 micrograms/mL or trough plasma concentrations greater than 5 to 10 micrograms/mL should be avoided. Dosage should be adjusted in all patients according to plasma-amikacin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284. As with some other aminoglycosides, once-daily dosage has been used successfully with amikacin without increasing toxicity, but local guidelines should be consulted (see also Once-daily Dosage, p.285).

A 0.25% solution has been instilled into body cavities in adults.

A liposomal formulation of amikacin is under investigation.

Preparations

BP 2008: Amikacin Injection;
USP 31: Amikacin Sulfate Injection.

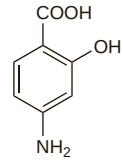
Proprietary Preparations (details are given in Part 3)
Arg.: Biklin; Greini; Riklinak; ***Austral.:*** Amikin; ***Austria:*** Biklin; ***Belg.:*** Amukin; ***Braz.:*** Amicacil†; Amicalin†; Amicilon; Aminocina†; Bactomicin†; Klebicil; Novamin; ***Canad.:*** Amikin†; ***Cz.:*** Amikin; Amikozit†; Miacin†; ***Fin.:*** Biklin; ***Fr.:*** Amiklin†; ***Ger.:*** Biklin; ***Gr.:*** Amicagel†; Amicasil; Amikan; Biorisan; Briklin; Cinegel; Durocin; Farcyclin; Flexelite; Fromentyl; Kancin-Gap; Lanomycin; Lifermycin; Likacin; Micalpha; Orlobin; Remikin; Roveniclin; Selaxa; Uzix; ***Hong Kong:*** Amikin; Apalin; Selemycin†; ***Hung.:*** Amikin; Likacin; ***India:*** Amcin; Amicin; Amicip; Mikacin; ***Indon.:*** Alostil; Amikin; Mikasin; ***Irl.:*** Amikin; ***Israel:*** Amikin†; ***Ital.:*** Amicasil; Amik; Amikan; BB-K8; Chemacin; Dramigel; Likacin; Lukadin; Mediamik; Migracin; Mikan; Mikavir; Nekacin; Pierami; ***Malaysia:*** Amikin†; Selemycin†; ***Mex.:*** Agnicin; Akacin; Amicina; Amikafur; Amikalem; Amikasons; Amikavi; Amikayect; Amikin; Amiyec; AMK; Baxi-K†; Beramikin; Biclin; Biokacin; Gamikal; Kafran; Kana; Karmikin; Libamic; Lisobac; Mikazul; Oprad; Plokim; Sermicina; Yectamid; ***Neth.:*** Amukin; ***NZ:*** Amikin; ***Philipp.:*** Amikacide; Amikin; Cidacid; Cinmik; Kamin; Kormakin; Nica; ***Pol.:*** Amikin; Biodacyna; ***Port.:*** Amic; Biclin; Kamina; ***Rus.:*** Amikozit (Амикозит); Selemycin (Селемицин); ***S.Afr.:*** Amikin; Kacinth-A; ***Singapore:*** Amikin; ***Spain:*** Biclin; Kanbine; ***Swed.:*** Biklin; ***Switz.:*** Amikin; ***Thai.:*** Akacin; Akicin; Amikasol†; Amikin; Anbikin; Siamik; Tipkin; Tybikin; ***Turk.:*** Amiketem; Amiklin; Amikozit; Mikasin; ***UAE:*** Mikacin; ***UK:*** Amikin; ***USA:*** Amikin; ***Venez.:*** Amikavax; Amikayect†; Behkacin; Biklin; Likacin.

Aminosalicylic Acid

Acidum Aminosalicylicum; Aminosalicílico, ácido; 4-Aminosalicylic Acid; Aminosalicylsyra; Aminosalisyylihappo; Aminosalylum; Para-aminosalicylic Acid; PAS; Pasalicylum. 4-Amino-2-hydroxybenzoic acid.

Аминосалициловая Кислота

$C_7H_7NO_3$ = 153.1.
CAS — 65-49-6.
ATC — J04AA01.
ATC Vet — QJ04AA01.



NOTE. Distinguish from 5-aminosalicylic acid (Mesalazine, p.1745).

Pharmacopoeias. In *US*.
USP 31 (Aminosalicylic Acid). A white or practically white, bulky powder that darkens on exposure to light and air; it is odourless or has a slight acetous odour. Slightly soluble in water and in ether; soluble in alcohol; practically insoluble in benzene. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a saturated solution in water is between 3.0 to 3.7. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Calcium Aminosalicylate

Aminosalicilato cálcico; Aminosalicylate calcium; Aminosalylcalcium; Aminosalylkalcium; Aminosalyylikalsium; Calcii Aminosalicylas; Calcii Para-aminosalicylas; Calcium PAS; Kalciumaminosalicylat; Kalsiumaminosalisylaatti. Calcium 4-amino-2-hydroxybenzoate trihydrate.

Аминосалицилат Кальция

$(C_7H_6NO_3)_2Ca,3H_2O$ = 398.4.
CAS — 133-15-3 (anhydrous calcium aminosalicylate).
ATC — J04AA03.
ATC Vet — QJ04AA03.

Pharmacopoeias. *Jpn* includes the heptahydrate.

Sodium Aminosalicylate

Aminosalicilato sódico; Aminosalicylan sodný dihydrát; Aminosalicylate Sodium; Aminosalylnatrium; Monosodium 4-Aminosalicylate Dihydrate; Natrii Aminosalicylas; Natrii aminosalicylas dihydricus; Natrii Paraaminosalicylas; Natrii Para-aminosalicylas; Natrio aminosalicilatas dihidratas; Natriumaminosalicylat; Natriumaminosalicylatdihydrat; Natriumaminosalisylaatti; Natriumaminosalisylaattidihydraatti; Pasalicylum Solubile; Sodium (aminosalicylate de) dihydraté; Sodium Para-aminosalicylate; Sodium PAS; Sodu aminosalicylan. Sodium 4-amino-2-hydroxybenzoate dihydrate.

Аминосалицилат Натрия

$C_7H_6NNaO_3,2H_2O$ = 211.1.
CAS — 133-10-8 (anhydrous sodium aminosalicylate); 6018-19-5 (sodium aminosalicylate dihydrate).
ATC — J04AA02.
ATC Vet — QJ04AA02.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), and *US*.
Ph. Eur. 6.2 (Sodium Aminosalicylate Dihydrate). A slightly hygroscopic, white or almost white, crystalline powder, or white or almost white crystals. Freely soluble in water; sparingly soluble in alcohol, practically insoluble in dichloromethane. A 2% solution in water has a pH of 6.5 to 8.5. Store in airtight containers. Protect from light.
USP 31 (Aminosalicylate Sodium). A white to cream-coloured, practically odourless crystalline powder. Soluble 1 in 2 of water; sparingly soluble in alcohol; very slightly soluble in chloroform and in ether. Its solutions decompose slowly and darken in colour. Prepare solutions within 24 hours of use. Under no circumstances should a solution be used if its colour is darker than that of a freshly prepared solution. pH of a 2% solution in water is between 6.5 and 8.5. Store in airtight containers at a temperature not exceeding 40°. Protect from light.

Stability. Aqueous solutions of aminosalicylates are unstable and should be freshly prepared.

Solutions of sodium aminosalicylate in sorbitol or syrup degraded more quickly to *m*-aminophenol than those in glycerol or propylene glycol.[1] Colour developed in all solutions but was not found to be an accurate indicator of decomposition of sodium aminosalicylate as it reflected only oxidation of *m*-aminophenol.

1. Blake MI, *et al*. Effect of vehicle on the stability of sodium aminosalicylate in liquid dosage forms. *Am J Hosp Pharm* 1973; **30:** 441–3.

Adverse Effects and Treatment

Aminosalicylic acid and its salts may cause the adverse effects of salicylates (see Aspirin, p.20).

Gastrointestinal effects are common and include nausea, vomiting, and diarrhoea; they may be reduced by giving doses with food or with an antacid but occasionally may be severe enough that therapy has to be withdrawn. Alteration of gastrointestinal function may lead to malabsorption of vitamin B_{12}, folate, and lipids.

Hypersensitivity reactions have been reported in 5 to 10% of adults, usually during the first few weeks of treatment, and include fever, skin rashes; less commonly, arthralgia, lymphadenopathy, and hepatosplenomegaly may occur and, rarely, a syndrome resembling infectious mononucleosis. Other adverse effects which have been attributed to a hypersensitivity reaction to aminosalicylate include jaundice and encephalitis. Blood disorders reported include haemolytic anaemia in patients with G6PD deficiency, agranulocytosis, eosinophilia, leucopenia, and thrombocytopenia. Psychosis may occasionally occur. Prolonged treatment may induce goitre and hypothyroidism. Crystalluria may occur.

Effects on the liver. Drug-induced hepatitis occurred in 0.32% of 7492 patients receiving antituberculous drugs; aminosalicylic acid was the most common cause.[1]

1. Rossouw JE, Saunders SJ. Hepatic complications of antituberculous therapy. *Q J Med* 1975; **44:** 1–16.

Precautions

Aminosalicylic acid and its salts should be used with great care in patients with hepatic or renal impairment and in patients with gastric ulcer. They should be given with caution to patients with G6PD deficiency. The sodium salt should be used with caution in patients with heart failure.

Aminosalicylates interfere with tests for glycosuria using copper reagents and for urobilinogen using Ehrlich's reagent.

Breast feeding. Small amounts of aminosalicylic acid are present in breast milk. A maximum concentration of 1.1 microgram/mL has been reported in the breast milk of a lactating woman 3 hours after a 4-g dose of aminosalicylic acid.[1]

1. Holdiness MR. Antituberculosis drugs and breast feeding. *Arch Intern Med* 1984; **144:** 1888.

Pregnancy. The use of aminosalicylic acid or its salts is not recommended in pregnant patients due to gastrointestinal intolerance.[1] In addition it has been noted that, a study published in 1964 suggested that first-trimester exposure may be associated with congenital defects although other studies had not found similar effects.[2]

1. Snider D. Pregnancy and tuberculosis. *Chest* 1984; **86:** 10S–13S.
2. Briggs GG, *et al*. *Drugs in pregnancy and lactation.* 7th ed. Philadelphia: Lippincott Williams and Wilkins, 2005: 59.

Interactions

The adverse effects of aminosalicylates and salicylates may be additive. Probenecid may also increase toxicity by delaying renal excretion and enhancing plasma concentrations of aminosalicylate. The activity of aminosalicylic acid may be antagonised by ester-type local anaesthetics such as procaine.

Antimicrobial Action

Aminosalicylic acid is bacteriostatic and is active against *M. tuberculosis*. Other mycobacteria are usually resistant. It has a relatively weak action compared with other antituberculous drugs. Resistance develops quickly if aminosalicylic acid is used alone.

◊ References.

1. Rengarajan J, *et al*. The folate pathway is a target for resistance to the drug para-aminosalicylic acid (PAS) in mycobacteria. *Mol Microbiol* 2004; **53:** 275–82.

Pharmacokinetics
When given orally, aminosalicylic acid and its salts are readily absorbed, and peak plasma concentrations occur after about 1 to 4 hours.

Aminosalicylate diffuses widely through body tissues and fluids, although diffusion into the CSF occurs only if the meninges are inflamed. About 15% of the sodium salt, and 50 to 70% of the acid, is bound to plasma proteins.

Aminosalicylate is metabolised in the intestine and liver primarily by acetylation. Urinary excretion is rapid, and 80% or more of a dose is excreted within 24 hours; 50% or more of the dose is excreted as the acetylated metabolite. The half-life of aminosalicylic acid is about 1 hour.

Aminosalicylate is distributed into breast milk (see under Precautions, above, for more details).

Uses and Administration
Aminosalicylic acid and its salts are second-line antimycobacterials given orally in the treatment of multidrug-resistant **tuberculosis** (p.196). They should always be given with other antituberculous drugs.

Aminosalicylic acid may be given as the acid or as the sodium salt. Sodium aminosalicylate 1.38 g is equivalent to about 1 g of aminosalicylic acid. However, a usual daily oral dose is 12 g in 3 divided doses and has been recommended for products containing the acid as well as for those containing the sodium salt.

For details of doses in infants, children, and adolescents, see below.

Aminosalicylate sodium is also given rectally in the treatment of **ulcerative colitis** in a usual dose of 2 g once daily.

Attempts have been made in formulation to overcome the bulk and exceedingly unpleasant taste of the aminosalicylates. The salts appear to be better tolerated than the free acid and solutions in iced water prepared immediately before use may be less unpleasant to take.

Administration. A small study suggested that giving aminosalicylic acid in a dose of 4 g twice daily produced adequate serum concentrations (well in excess of 1 microgram/mL, a typical MIC against *Mycobacterium tuberculosis*) for up to 12 hours after each dose.[1] The drug was taken with an acidic beverage such as fruit juice to prevent early release in the stomach. A single 4-g dose was not sufficient to maintain serum concentrations for the full 24-hour dosage interval. The authors had subsequently changed their practice to use a twice-daily regimen for aminosalicylic acid in patients with multidrug-resistant tuberculosis.

1. Peloquin CA, *et al*. Once-daily and twice-daily dosing of p-aminosalicylic acid granules. *Am J Respir Crit Care Med* 1999; **159:** 932–4.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) and WHO suggest an oral dose of para-aminosalicylic acid 200 to 300 mg/kg 2 to 4 times daily, to a maximum dose of 10 g daily.

Administration in renal impairment. It has been recommended that aminosalicylic acid should be avoided in patients with renal impairment.[1] An increase in plasma clearance of aminosalicylic acid (attributed to increased hepatic metabolism) has been noted in patients with renal impairment, hence attempting to give aminosalicylate in reduced doses to such patients may lead to subtherapeutic serum concentrations.[2]

1. Appel GB, Neu HC. The nephrotoxicity of antimicrobial agents (first of three parts). *N Engl J Med* 1977; **296:** 663–70.
2. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984; **9:** 511–44.

Inflammatory bowel disease. Together with corticosteroids, derivatives of 5-aminosalicylic acid are one of the mainstays of the treatment of inflammatory bowel disease (p.1697). However, aminosalicylic acid (4-aminosalicylic acid) has also been investigated, and beneficial results have been reported with both enemas[1-4] and oral dose forms[5] in ulcerative colitis. Three patients who developed acute pancreatitis while taking mesalazine (5-aminosalicylic acid) for inflammatory bowel disease, later tolerated treatment with 4-aminosalicylic acid enemas.[6]

1. Campieri M, *et al*. 4-Aminosalicylic acid (4-ASA) and 5-aminosalicylic acid (5-ASA) in topical treatment of ulcerative colitis patients. *Gastroenterology* 1984; **86:** 1039.
2. Ginsberg AL, *et al*. Treatment of left-sided ulcerative colitis with 4-aminosalicylic acid enemas: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 195–9.
3. Sharma MP, Duphare HV. 4-Aminosalicylic acid enemas for ulcerative colitis. *Lancet* 1989; **i:** 450.
4. O'Donnell LJD, *et al.* Double blind, controlled trial of 4-aminosalicylic acid and prednisolone enemas in distal ulcerative colitis. *Gut* 1992; **33:** 947–9.
5. Beeken W, *et al*. Controlled trial of 4-ASA in ulcerative colitis. *Dig Dis Sci* 1997; **42:** 354–8.
6. Daniel F, *et al*. Tolerance of 4-aminosalicylic acid enemas in patients with inflammatory bowel disease and 5-aminosalicylic-induced acute pancreatitis. *Inflamm Bowel Dis* 2004; **10:** 258–60.

Manganese toxicity. Intravenous aminosalicylic acid, given in a course of 6 g daily for 4 days a week, for fifteen courses, produced significant benefit in a patient with parkinsonism induced by chronic occupational manganese exposure.[1] The patient remained well on prolonged follow-up. Other cases of benefit had been reported in the Chinese literature.

1. Jiang Y-M, *et al*. Effective treatment of manganese-induced occupational Parkinsonism with p-aminosalicylic acid: a case of 17-year follow-up study. *J Occup Environ Med* 2006; **48:** 644–9.

Preparations
USP 31: Aminosalicylate Sodium Tablets; Aminosalicylic Acid Tablets.

Proprietary Preparations (details are given in Part 3)
Canad.: Nemasol†; ***Chile:*** Aflogol; ***Cz.:*** Quadrasa†; ***Fr.:*** Quadrasa; ***Ger.:*** Pas-Fatol N; ***Ital.:*** Quadrasa†; Salf-Pas; ***Port.:*** Paramino-Corazida; ***Rus.:*** Pask-Akri (Паск-Акри); ***Switz.:*** Perfusion de PAS†; ***Thai.:*** PAS Sodium; ***Turk.:*** PAS; ***USA:*** Paser.

Multi-ingredient: ***India:*** Inapas.

Amoxicillin *(BAN, rINN)*

Amoksisilin; Amoksisilliini; Amoxicilina; Amoxicilline; Amoxicillinum; Amoxycillin. (6*R*)-6-[α-D-(4-Hydroxyphenyl)glycylamino]penicillanic acid.

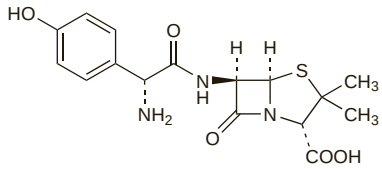
Амоксициллин

$C_{16}H_{19}N_3O_5S$ = 365.4.

CAS — 26787-78-0.

ATC — J01CA04.

ATC Vet — QG51AX01; QJ01CA04.



Amoxicillin Sodium *(BANM, USAN, rINNM)*

Amoksicilino natrio druska; Amoksisilin Sodyum; Amoksisilliininatrium; Amoksycylina sodowa; Amoxicilin sodná sůl; Amoxicilina sódica; Amoxicilline sodique; Amoxicillinnatrium; Amoxicillinátrium; Amoxicillinum natricum; Amoxycillin Sodium; BRL-2333AB-B; Natrii Amoxicillinum.

Натрий Амоксициллин

$C_{16}H_{18}N_3NaO_5S$ = 387.4.

CAS — 34642-77-8.

ATC — J01CA04.

ATC Vet — QJ01CA04.

Pharmacopoeias. In *Chin.* and *Eur.* (see p.vii).
Ph. Eur. 6.2 (Amoxicillin Sodium). A white or almost white, very hygroscopic powder. Very soluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 8.0 to 10.0. Store in airtight containers.

Amoxicillin Trihydrate *(BANM, rINNM)*

Amoksicilinas trihidratas; Amoksisilin Trihidrat; Amoksisilliinitrihydraatti; Amoksycylina trójwodna; Amoxicilin trihydrát; Amoxicilina trihidrato; Amoxicillin *(USAN)*; Amoxicilline trihydratée; Amoxicillin-trihidrát; Amoxicillintrihydrat; Amoxicillinum trihydricum; Amoxycillin Trihydrate; BRL-2333.

Амоксициллин Тригидрат

$C_{16}H_{19}N_3O_5S,3H_2O$ = 419.4.

CAS — 61336-70-7.

ATC — J01CA04.

ATC Vet — QJ01CA04.

NOTE. Compounded preparations of amoxicillin may be represented by the following names:

- Co-amoxiclav *x/y* (*BAN*)—amoxicillin (as the trihydrate or the sodium salt) and potassium clavulanate; *x* and *y* are the strengths in milligrams of amoxicillin and clavulanic acid respectively
- Co-amoxiclav (*PEN*)—amoxicillin trihydrate and potassium clavulanate.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Int., Jpn, US,* and *Viet.*
Ph. Eur. 6.2 (Amoxicillin Trihydrate). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol; practically insoluble in fatty oils. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 0.2% solution in water has a pH of 3.5 to 5.5. Store in airtight containers.
USP 31 (Amoxicillin). A white, practically odourless crystalline powder. Slightly soluble in water and in methyl alcohol; insoluble in carbon tetrachloride, in chloroform, and in benzene. pH of a 0.2% solution in water is between 3.5 and 6.0. Store in airtight containers.

Adverse Effects and Precautions
As for Ampicillin, p.204.

The incidence of diarrhoea is less with amoxicillin than ampicillin.

Hepatitis and cholestatic jaundice have been reported with amoxicillin plus clavulanic acid; the clavulanic acid component has been implicated. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis have also been attributed occasionally to the use of amoxicillin with clavulanic acid.

Breast feeding. Although amoxicillin is excreted in breast milk in small amounts,[1] the American Academy of Pediatrics considers that it is usually compatible with breast feeding.[2]

1. Kafetzis DA, *et al.* Passage of cephalosporins and amoxicillin into the breast milk. *Acta Paediatr Scand* 1981; **70:** 285–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/05/04)

Effects on the liver. Hepatitis and cholestatic jaundice associated with the combination amoxicillin with clavulanic acid (co-amoxiclav) have been reported[1-4] and by 1993 the UK CSM had received 138 reports of hepatobiliary disorders, 3 of which were fatal.[5] It warned that, although usually reversible, the reaction often occurred after stopping therapy with a delay of up to 6 weeks. It appeared that the clavulanic acid was probably responsible. Retrospective analysis of cases reported in Australia[6] and a cohort study in the UK[7] found increasing age and prolonged treatment to be major risk factors for jaundice after co-amoxiclav; male sex is also a risk factor. By 1997 the CSM considered that cholestatic jaundice occurred with a frequency of about 1 in 6000 adult patients and that the risk of acute liver injury was about 6 times greater with co-amoxiclav than with amoxicillin alone. Therefore it recommended that co-amoxiclav should be reserved for bacterial infections likely to be caused by amoxicillin-resistant strains, and that treatment should not usually exceed 14 days.[8]

1. Stricker BHC, *et al.* Cholestatic hepatitis due to antibacterial combination of amoxicillin and clavulanic acid (Augmentin). *Dig Dis Sci* 1989; **34:** 1576–80.
2. Wong FS, *et al.* Augmentin-induced jaundice. *Med J Aust* 1991; **154:** 698–701.
3. Larrey D, *et al.* Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases. *Gut* 1992; **33:** 368–71.
4. Hebbard GS, *et al.* Augmentin-induced jaundice with a fatal outcome. *Med J Aust* 1992; **156:** 285–6.
5. Committee on Safety of Medicines/Medicines Control Agency. Cholestatic jaundice with co-amoxiclav. *Current Problems* 1993; **19:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 28/07/08)
6. Thomson JA, *et al.* Risk factors for the development of amoxycillin-clavulanic acid associated jaundice. *Med J Aust* 1995; **162:** 638–40.
7. Rodríguez LAG, *et al.* Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. *Arch Intern Med* 1996; **156:** 1327–32.
8. Committee on Safety of Medicines/Medicines Control Agency. Revised indications for co-amoxiclav (Augmentin). *Current Problems* 1997; **23:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023230&RevisionSelectionMethod=LatestReleased (accessed 11/07/06)

Effects on the teeth. A report of tooth discoloration in 3 children associated with the use of amoxicillin with clavulanic acid.[1]

1. Garcia-López M, *et al.* Amoxycillin-clavulanic acid-related tooth discoloration in children. *Pediatrics* 2001; **108:** 819–20.

Sodium content. Each g of amoxicillin sodium contains about 2.6 mmol of sodium.

Interactions
As for Ampicillin, p.204.

Antimicrobial Action
As for Ampicillin, p.204.

Amoxicillin has been reported to be more active *in vitro* than ampicillin against *Enterococcus faecalis, Helicobacter pylori,* and *Salmonella* spp., but less active against *Shigella* spp.

Amoxicillin is inactivated by beta lactamases and complete cross-resistance has been reported between amoxicillin and ampicillin. The spectrum of activity of amoxicillin may be extended by use with a beta-lactamase inhibitor such as clavulanic acid (p.250). As well as reversing resistance to amoxicillin in beta-lactamase-producing strains of species otherwise sensitive, clavulanic acid has also been reported to enhance the activity of amoxicillin against several species not generally considered sensitive. These have included *Bacteroides, Legionella,* and *Nocardia* spp., *Haemo-*